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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

APRIL 1944

THE POSTCHOLECYSTECTOMY SYNDROME AND ITS TREATMENT*

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REFINEMENTS in the technique of cholecystography have aided substantially in the accurate diagnosis of gallbladder disease. The recent improvements in the pre- and postoperative preparation of patients, together with the standardization of the surgical technique, have so lowered the operative mortality that cholecystectomy is a relatively safe procedure. Unfortunately, the results revealed by follow-up examinations after operation, especially in the group of patients with noncalculous cholecystitis, are far from satisfactory.[1,2,3,4] The causes of failure following cholecystectomy are many and the complaints which ensue may be bizarre.[5] Frequently the removal of the gallbladder is followed by acute symptoms identical to those which existed prior to operation. This postoperative symptom complex so characteristic of gallbladder disease is called the postcholecystectomy syndrome.

The postcholecystectomy syndrome may resemble cholecystitis and cholelithiasis in all their varied clinical manifestations and it may simu-

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TABLE I

END RESULTS OF OPERATION UPON THE GALLBLADDER AND COMMON DUCT[1]

Condition or Operation	*Cases Followed No.*	*Re-Operation No.*	*Well No.*	*Well After One Year No.*	*Well After Two Years No.*	*Total Well*		*Improved*		*Not Improved*	
						No.	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*
1. Cholecystectomy for Chronic Cholecystitis with Stones.	119	2	70	22	2	94	78.9	14	11.8	11	9.3
2. Cholecystectomy for Chronic Cholecystitis without Stones.	8	0	2	0	1	3	37.5	0	...	5	62.5
3. Cholecystostomy for Chronic Cholecystitis with Stones.	1	0	1	0	0	1	100	0	...	0	...
4. Cholecystectomy for Acute Cholecystitis with Stones.	75	5	48	11	2	61	81.3	4	5.3	10	13.3
5. Cholecystostomy for Acute Cholecystitis with Stones.	7	1	4	1	0	5	71.4	1	14.3	1	14.3
Total Operations on Gallbladder.	210	8	125	34	5	164	78.1	19	9.0	27	12.9
6. Choledochostomy with Operation on Gallbladder.	12	2	6	0	2	8	66.7	1	8 3	3	25.0
7. Choledocholithotomy with Operation on Gallbladder	31	7	18	4	3	25	80.6	2	6.5	4	12.9
Total Operations on Gallbladder and Common Duct.	43	9	24	4	5	33	76.5	3	7.2	7	16.3

late many of the physical findings. The acute symptoms sometimes occurring during the convalescent period and most frequently noted during the first two years may be heralded by agonizing colic confined to the upper half of the abdomen, often radiating to either shoulder or the interscapular region. These attacks are commonly accompanied by nausea and vomiting, and are often associated with transient periods of mild jaundice, pruritus, and occasionally intermittent fever and chills. Physical examination may reveal abdominal soreness and occasionally a tinge of icterus.

Hellström,[6] reporting one thousand and forty-one cases in which cholecystectomy had been done, stated that about 30 per cent of the patients complained of upper abdominal pain and distressing pressure. The symptoms were similar in nature to the colicky attacks described prior to cholecystectomy. In only nine of the cases were the episodes due to residual ductal calculi, and in a few of the patients the attacks terminated in an acute pancreatitis. However, in the majority of cases Hellström offered no explanation which would account for the occurrence of the postcholecystectomy colic.

Doubilet,[7] in the Surgical Clinic of The Mount Sinai Hospital, personally interviewed two hundred and fifty-three patients following operations for gallbladder disease and saw them at regular intervals during periods varying from one to seven years. The end results are summarized in Table I. Practically 40 per cent of all patients who were followed suffered from postoperative symptoms, either temporary or permanent. The majority of this group described the acute episodes as resembling those which had existed prior to operation and in some cases the attacks were frequent and severe enough to require sedation. The pains were of two main types. In the larger group, seventy-eight patients stated that the intense postprandial pain lasted from five minutes to two hours and occasionally radiated to the back. In a smaller group comprising twenty-four patients the pain which lasted from two to twenty-four hours radiated from the left upper quadrant to the shoulders. It was frequently accompanied by persistent abdominal soreness and in two cases an acute pancreatitis developed. In our experience these symptoms might follow the surgical removal of any gallbladder regardless of its pathologic lesions. The postcholecystectomy syndrome was most frequent in those cases characterized by definite colic prior to operation and in which functional disturbances were

demonstrated by cholecystography, but in which surgical exploration revealed the absence of pathologic lesions of the gallbladder or the presence of a noncalculous cholecystitis. It seemed less frequent in cases of calculous cholecystitis. The syndrome was relatively rare when a fibrosed functionless gallbladder and dilated common duct were present.

The etiology of the postcholecystectomy syndrome may usually be attributed to a dyskinesia of the sphincter mechanism. This sphincter spasm may be stimulated either by local causes or by intrabiliary factors such as recurrent or residual calculosis of the cystic or common bile duct, partial traumatic strictures of the choledochus, cholangitis or pancreatitis. In some cases the dyssynergia may be initiated by psychic disturbances or by glandular dyscrasias, and in others it may be the result of a spastic colon. The significance and importance of biliary dyskinesia has been thoroughly reviewed by Ivy, Goldman and Sandblom,[8,9] Hill,[10] and Bergh and Layne.[11] It will only be necessary here to consider certain fundamental anatomic, physiologic and pathologic data which are concerned in the mechanism and production of most cases of postcholecystectomy syndrome. The anatomy of the periampullary region of the duodenum has been extensively investigated by Letulle and Nathan-Larrier,[12] Giordano and Mann,[13] and others, and has recently been examined from an embryologic standpoint by Boyden and his associates.[14,15] (Fig. 1) The latter have identified longitudinal fasciculi which probably served to erect the papilla and aid in the ejection of bile, a sphincter of the pancreatic duct, a definite sphincter at the terminal end of the choledochus, and in addition a sphincter of the ampulla which was found in about one-sixth of their dissections. The contraction of this muscle, while it prevents the flow of secretions into the duodenum, converts the choledochus and the pancreatic duct into one canal so that bile may pass into the pancreatic duct and pancreatic secretions may pass into the common bile duct. The pathologic significance of this, which is extremely important, will be subsequently discussed. Not only is the sphincter of the common bile duct a distinct anatomic entity, but Bergh[16] has presented evidence to show that it acts independently of the duodenal musculature to which it is intimately connected. However, functionally the sphincter mechanism includes both the intrinsic muscles of the papilla and the associated muscles of the adjacent intestinal wall. It prevents the regurgitation of duodenal contents, aided by the oblique entrance of

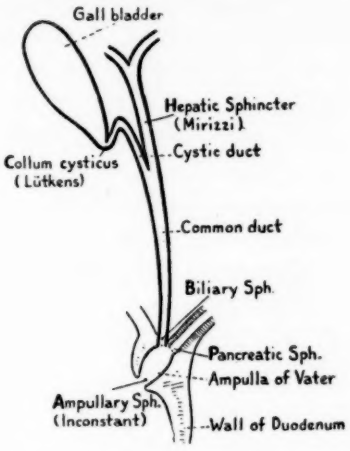


Fig. 1—Location of the sphincters of the biliary and pancreatic ducts.

the choledochus through the wall of the duodenum and by the folds of mucous membrane in the ampulla. The sphincter is most important in its relationship to the physiology of the gallbladder. When the sphincter is contracted between the periods of gastric digestion the normal gallbladder through its absorptive ability and elasticity concentrates and stores large amounts of bile which are continuously being secreted by the liver. The gallbladder acts as a pressure regulating apparatus and insures a continuation of bile secretion by preventing the intraductal pressure in the biliary tree from exceeding the secretory pressure of the liver. The intermittent discharge of bile into the intestine is dependent upon the relaxation of the sphincter mechanism and the simultaneous contraction of the intrinsic musculature of the gallbladder wall according to the Meltzer law of reciprocal innervation. The exact mechanism is not clear and has recently been questioned.[17] However, it is quite understandable that any gradual increase in the tonicity of the sphincter due to reflex causes may cause a stasis of bile, and due to the apparent lack of elasticity of the common bile duct may lead to dilatation of the gallbladder resulting in a hypotonic organ.[18] If, however, the gallbladder musculature responds with increased activity, a hypertonic type of gallbladder may develop. On the other hand, a sudden tonic spasm of the sphincter of Oddi which precipitates a

rapid increase in the intraductal pressure of the common bile duct, or a sudden distention of the gallbladder may cause an acute colic. Lütkens[19] described another sphincter located at the neck of the gallbladder, so-called collum cysticus, as being present in about 75 per cent of his cases. While his original observations were doubted by many, recent cholecystographic evidence affords positive proof of its existence.[10] Sudden spasm of this sphincter may, too, be another cause of gallbladder colic. Recently Mirizzi,[20] from cholangiographic studies, has described a physiologic sphincter at the level of the hepatic duct, a spasm of which may cause hepatic pain and transient jaundice. It becomes quite evident that spasm of any of these sphincters may result in an increase of intraductal pressure sufficient in intensity to produce colic. For this reason the removal of the gallbladder, especially the hypostatic, noncalculous type, may give little clinical relief because the original source of the symptomatology may have been a spasm of the sphincter of the common bile duct or the ampulla. In other cases the removal of an apparently innocuous gallbladder together with the cystic duct is occasionally followed by a complete disappearance of the symptoms. The colic may have been due to a reflex spasm of the collum cysticus impeding the free emptying of an actively contracting gallbladder. It is also likely that the normal activity of the sphincter may be simultaneously altered when once acute or chronic pathologic changes in the gallbladder have interfered with its physiologic functions. Clinically it is not unusual to observe jaundice in acute cholecystitis with or without stones and yet at operation to find no organic obstructive cause for the icterus. This transient jaundice is probably due to an obstruction caused by a temporary spasm of the sphincter. Inasmuch as the physiologic activity of the gallbladder and the various sphincter mechanisms are so intimately correlated, cholecystectomy for cholecystitis with or without calculi will invariably be followed by alterations in the sphincter mechanism and in the pathologic physiology of the common bile duct. What these changes are is still a matter of controversy. Some believe that following the removal of the gallbladder the sphincter may lose its tone and the common bile duct may dilate. Puestow[21] predicates this mainly upon the low intraductal pressure following cholecystectomy and the relief of symptoms produced by operation. This viewpoint has not been generally accepted. Judd and Mann[22] have noted dilatation of the common bile duct after cholecys-

tectomy in animals. Colp, Doubilet and Gerber[23] have reported that following section of the sphincter in some cholecystectomized dogs there is a diminution in the caliber of the duct and a reduction in the intraductal pressure. Bergh and Layne,[11] McGowan, Butsch and Walters,[24] and Doubilet and Colp[25] have demonstrated clinically by manometric readings and lipiodol injections of the intubated choledochus that immediate postoperative resistance is offered by the sphincter and that marked spasm may be produced by pharmacologic agents. Moreover, any sudden distention of the intubated choledochus may initiate severe colic. In fact, in some cases reoperated for a calculous obstruction years after cholecystectomy had been performed, an irritable spastic sphincter was suspected because of the high manometric readings obtained from the intubated, dilated and infected choledochus. Definite hypertrophy of the muscles about the ampulla, even to the point of stenosis, has been observed following cholecystectomy by Bergh,[16] Westphal,[26] del Valle[27] and others. These experimental and clinical observations all tend to support the existence of spasm of the sphincter of Oddi and lend support to the current concept that biliary dyskinesia is an instrumental factor, not only in the causation of gallbladder disease, but in the production of the acute and uncertain symptomatology subsequent to cholecystectomy. The fact that many patients gain eventual relief and few suffer severely from the postcholecystectomy syndrome may be explained in part by the gradual physiologic adaptations of the sphincters and the extra-hepatic bile ducts to the loss of the gallbladder. For, as Ivy has so aptly suggested, there is no reason to assume that the sphincter mechanism reacts the same in all cases; a sphincter which may have been spastic in the immediate postoperative period may lose its spasticity for a time and then regain it later. This may account for the occurrence of colic during convalescence, and its eventual disappearance following appropriate medical treatment. The persistence of the postcholecystectomy syndrome in other cases may be due to dyskinesia of the sphincter of Oddi secondary to intraductal organic disturbances such as recurrent or residual cystic and choledochal calculosis, cholangitis, or stricture formation. But the activity of the sphincter mechanism may cause other complications in the presence of the ampullary sphincter. A contraction of this muscle converts the common bile duct and the duct of Wirsung into one canal so that, depending upon the relative secretory pressure, bile may flow into the

pancreatic duct or pancreatic ferments may mix with bile in the choledochus. The admixture of pancreatic juice with bile in the choledochus is fairly frequent. It may be perfectly innocuous. We[28] were able to demonstrate the presence of pancreatic ferments in about 28 per cent of a series of sixty cases in which specimens of bile were obtained from the intubated choledochus. In this particular series the pancreatic reflux was due solely to a spasm of the ampullar sphincter. The pathologic effects of this phenomenon have been proven by the experimental evidence and clinical investigations of Westphal, Popper, Wolfer and others.[26] The evidence is now quite clear that pancreatic reflux may cause either a nonperforative bile peritonitis or an acute chemical cholecystitis. In a series of fourteen consecutive cases of acute cholecystitis the gallbladder bile contained pancreatic ferments which probably were the agents responsible for the acute chemical inflammation. It is possible that some cases of chronic cholecystitis and chronic choledochitis with or without stones may be the result of an intermittent pancreatic reflux. It has been appreciated since Opie, in 1906, reported his classic case of a biliary calculus occluding the ampulla that a retrojection of infected bile may cause an edema or an acute pancreatitis. The pathogenesis of this condition has been fully described by Dragstedt and his coworkers.

Dyskinesia of the ampullary sphincter following cholecystectomy may play a significant and important role in the clinical picture of the postcholecystectomy syndrome. Our follow-up studies in those cases in which the presence of a pancreatic reflux was proven have disclosed no clinical evidence upon which changes in the common bile duct could be predicated. Whipple reported three cases of irreparable stricture of the choledochus in which he felt sure that the common bile duct had not been injured at the time of the primary cholecystectomy. When these patients had become deeply jaundiced requiring a second operation nothing was found but a shred of dense connective tissue extending from the duodenum to the portal fissure. He felt that such an extensive destruction of the common bile duct could only be explained by an activated pancreatic reflux. It is barely possible that those cases of chronic choledochitis described by the French surgeons in which the common bile duct resembles a pipe stem, and into which a fine probe could not be introduced, may be due to repeated pancreatic reflux rather than to biliary stagnation.

The effects of postcholecystectomy biliary reflux are known. El-

man[29] and others have called attention to recurrent attacks of acute pancreatitis and pancreatic edema following cholecystectomy and have demonstrated an elevation of the blood amylase during the acute phase. It is more than likely that biliary reflux as a result of sphincter spasm accounted for the acute attacks of pain in the left upper quadrant which left a distinct soreness in the twenty-four cholecystectomized patients already described. Two of these cases eventually developed an acute pancreatitis.

The facts which have been presented seem to show that a dyskinesia of the sphincter mechanism contributes materially to the production of certain types of gallbladder disease and acts as a dominant factor in the production of the postcholecystectomy syndrome. The medical treatment therefore in both conditions is essentially the same. It should always be tried before surgery is advised. Little new has been added to the well recognized therapy of biliary colic. It is still customary to give morphine in adequate doses. This gives relief by blocking the higher nerve centers, but it simultaneously increases the muscle spasm of the sphincter mechanism to such a degree that pain often continues when the effect of the opiate has worn off. Small hypodermic doses of morphine may be used as a therapeutic test to substantiate a diagnosis of dyskinesia. It will often cause a tonic spasm of an irritable sphincter with an increase in the intraductal pressure sufficient to cause an attack simulating gallbladder colic. In some of these instances nitroglycerine may afford relief. However, even if this test is positive it does not rule out intraductal pathologic lesions which we have seen may contribute to the picture either of gallbladder disease or the postcholecystectomy syndrome. Antispasmodics such as amylnitrate, glycerol trinitrate, or theophylline, and others should be ideal pharmacologic agents. Unfortunately they are not always successful in relaxing a spastic sphincter. Best and Barr[30] feel that although the action of atropine is not constant, it is occasionaly effective. They recommend that if a combination of morphine and atropine does not give relief in three hours additional morphine by hypodermic injection and nitroglycerine by mouth should be tried.

Each patient complaining of gallbladder colic should be thoroughly examined in order to determine the factor producing the biliary dyskinesia. It is important to identify and neutralize if possible the precipitating causes. Pavel[31] has emphasized the importance of the psyche

in the production of biliary dyskinesia. During periods of intense emotional excitement sphincter spasm may become so severe as to produce jaundice and pain. This nervous instability, especially in female patients, is frequently combined with irregularities in menstruation and with symptoms of menopause. In cases such as these, relief has been obtained by the administration of sedatives and proper hormonal therapy. A spastic colon, too, undoubtedly plays a major role in the reflex production of right upper quadrant symptoms. Lahey and Jordan[32] have reported that in a series of sixty-five cases, 44 per cent of the patients whose gallbladders could not be visualized with dye showed filling of the organ after a period devoted to the active treatment of their constipation. In the present series of patients, 57 per cent gave a history of constipation prior to operation. Some cases were improved following cholecystectomy but only 37 per cent were cured. The administration of bile salts in adequate amounts, the judicious use of mineral oil and magnesium sulfate and daily enemata of sodium carbonate often lessened the distressing right upper quadrant symptoms. Dyspepsia which was present in 67 per cent of our patients was relieved in 42 per cent of the cases. Efforts were made to ameliorate these distressing symptoms. Measures were prescribed to induce the frequent relaxation of the sphincter and to avoid periods of tonic contraction. Patients were advised to eat bland and non-irritating foods and to take small meals at frequent intervals, for periods of gastric digestion are followed by a discharge of bile into the duodenum. By this simple expedient, biliary stagnation may be prevented. It has also been shown by Doubilet and Colp[25] that when hydrochloric acid in high concentration reaches the duodenum the increased acidity intensifies the tonus of the sphincter. Therefore, if a test meal disclosed evidences of hyperchlorhydria, anacids were unhesitatingly prescribed to lower gastric acidity in an attempt to diminish sphincter tone. In some cases in which the symptoms of dyskinesia were severe, lavage of the duodenum with magnesium sulfate appeared to relax the sphincter. These therapeutic and dietary measures were found to be effective in relieving the postcholecystectomy syndrome in most patients. In about 8 per cent of the cases the symptoms persisted regardless of treatment. When the attacks became increasingly severe, or were complicated by the presence of biliary obstruction or cholangitis, surgery was advised.

Exploration was usually performed under spinal anesthesia, because

it afforded the most complete muscular relaxation. In these secondary operations it was quite usual to find the omentum, colon, pylorus and duodenum distorted and bound to the under surface of the liver. These firm and dense adhesions may have contributed in part to the symptomatology. The stomach and duodenum were always meticulously examined for the presence of peptic ulcer. The fact that patients have had a cholecystectomy does not eliminate the possibility that an ulcer may have been overlooked or may have developed in the interim. Following the lysis of adhesions the identification of the foramen of Winslow, the stump of the cystic duct, and the choledochus did not present unusual difficulties unless these structures had been partially obliterated by stricture. But any structure which was thought to be the duct was always first aspirated for the presence of bile. The specimen was subsequently examined microscopically, chemically and bacteriologically. The common duct was then opened and carefully probed, especially in its terminal portion, for it is here that impacted stones may be missed. Immediate cholangiography was not practiced. The pancreas, too, was carefully examined. Palpation was often misleading for the organ, while not enlarged, may be the seat of a chronic inflammation as proven by a punch biopsy. The operative findings in this series were found to be calculi in the stump of the cystic duct in two patients, and in the common duct in five patients; evidences of cholangitis were present in two cases and in two others an acute pancreatitis was found. In two patients a stricture of the papilla was encountered, and in seven cases no visible pathologic lesions were found which might account for the episodes of postcholecystectomy colic. The symptoms were therefore attributed to an intractable dyskinesia of the sphincter of Oddi.

Several surgical methods have been advocated to relieve sphincter spasm. Dilatation of the sphincter may be accomplished by passing graduated sounds through the common bile duct into the duodenum. It is a popular but not an entirely innocuous procedure. If the dilatation has been forceful and the sphincter mechanism has been unduly traumatized, an ascending anaerobic infection by Clostridium welchii may occur with fatal results. Biliary duodenal intubation has been recommended by Duval[33] and Walzel[34] to counteract the spastic sphincter. A T or straight tube is inserted via the common duct and the sphincter into the duodenum. This indwelling tube not only provides for the

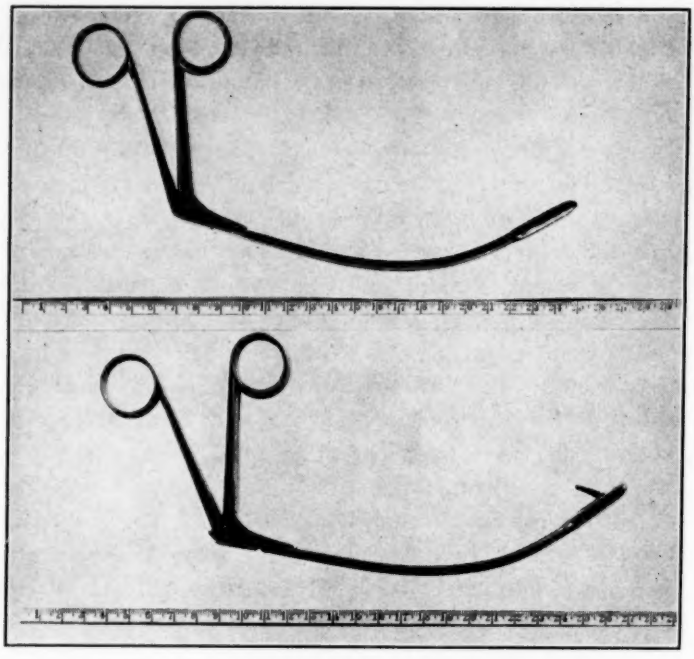


Fig. 2—The sphincterotome, closed and open.

immediate delivery of bile into the intestines but its mechanical presence maintains a continuous dilatation of the sphincter until the T tube is either withdrawn by the surgeon or the straight tube is eventually passed by the patient. Sasse,[35] Flörcken[36] and Petermann[37] have advised choledochoduodenostomy for either an obstructed or a spastic sphincter. An anastomosis between a dilated common bile duct and the contiguous duodenum certainly by-passes the sphincter mechanism. This procedure was proven to be most efficacious in the two cases of papillary stenosis in this series. However, choledochoduodenostomy, in addition to presenting certain technical difficulties, has another disadvantage. Theoretically, with the elimination of the sphincter mechanism there is the possibility of ascending infection by duodenal reflux. In spite of the fact that gastroduodenal roentgenograms in these patients often demonstrate the presence of barium or air in the common bile duct and its radicles, there is very little clinical evidence of cholangitis. The dilata-

tion of the sphincter, either by sounds or biliary duodenal intubation, is temporary and its effects are transitory. A dilated sphincter may eventually regain its tone and recurrent attacks of spasm may ensue. The result of choledochoduodenostomy is undoubtedly more permanent but the operative procedure has an appreciable mortality and a definite postoperative morbidity.

However, there is a direct surgical approach to the spastic sphincter. The sphincter of the common bile duct and sphincter of the ampulla if present may be paralyzed by surgical section of its fibers. This procedure has been done unwittingly since transduodenal choledochostomy was performed for impacted calculi, for it is impossible to extract the stones in these cases without first cutting the musculature of the sphincter mechanism. Archibald[38] was one of the first to divide the sphincter transduodenally for a dyskinesia. Del Valle[27] sectioned it through the duodenum for Odditis, a condition in which a retracted sphincter partially obstructed the flow of bile. Surgeons have been rather reluctant to deal directly with the sphincter in these unusual cases of intractable dyskinesia. It is quite difficult to identify the biliary papilla after the duodenum has been opened. But the papilla may be easily recognized if a large sized probe has first been introduced through the common bile duct into the region of the papilla. An incision through the anterior duodenal wall may then be made over this area. The sphincter musculature is easily divided under direct vision, following which the duodenostomy may be closed transversely. Recently Strode[39] described an effective and successful technique for transduodenal sphincterotomy in two cases of biliary dyskinesia. However, anterior duodenostomy may be followed by peritonitis, duodenal fistula and the physiologic disturbances due to duodenal adhesions. These complications may be obviated by endocholedochal sphincterotomy, a procedure in which the sphincter is divided by a specially designed instrument (Fig. 2) which has been introduced through the common bile duct. The experimental phase of this procedure has been described by Colp, Doubilet and Gerber[23] and the first case in which the operation was performed was reported in 1938.[40] Briefly, following a choledochostomy the patency of the papilla is first established by the passage of a fair sized probe into the duodenum. The closed sphincterotome is next introduced through the common bile duct and papilla into the duodenum. (Fig. 3). The sphincterotome is then opened, exposing the knife blade. The in-

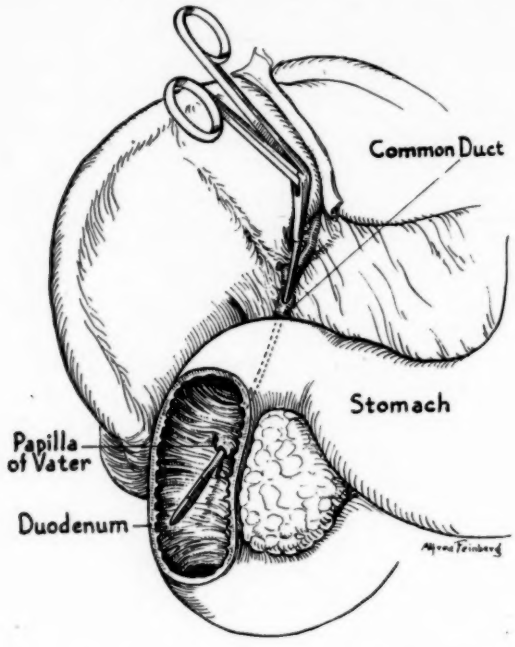
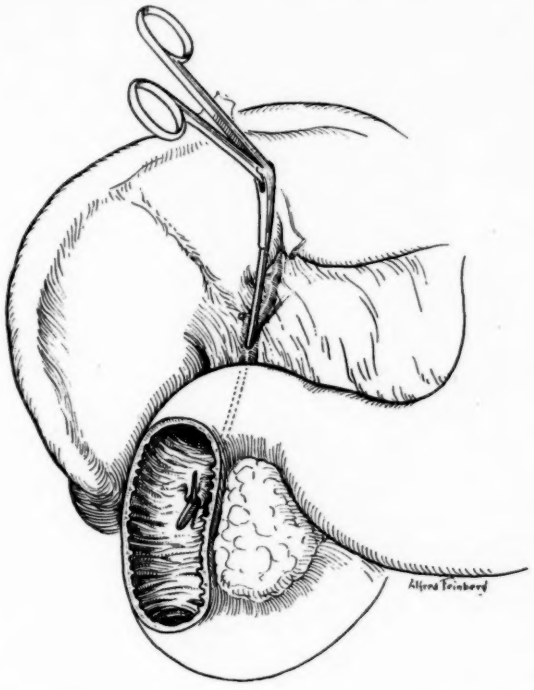


Fig. 3 — The closed sphincterotome is introduced through a cholecystectomy into the duodenum via the papilla of Vater.

strument is carefully withdrawn until the knife blade firmly impinges upon the sphincter. (Fig. 4). As the instrument is closed the knife is driven home, dividing the musculature, after which the sphincterotome may be easily withdrawn. The operation is simple and has not been followed by unusual bleeding. Often, upon opening the instrument, a specimen from the sphincter region may be found in the knife slot. The tissue thus obtained may be examined histologically. The common bile duct is then drained with a T tube. Drainage is important, not only because it provides an exit for bile if postoperative edema should develop in the region of the sphincter, but because it affords an opportunity for manometric readings and lipiodol studies. The drainage of the common bile duct is continued until the closure of the T tube is followed by the absence of pain and the presence of normal temperature. The postoperative course to date has been uneventful and no untoward sequelae developed which could possibly be attributed to the division of the



Fige. 4—The sphincterotome is opened and withdrawn until it firmly impinges upon the papilla of Vater.

sphincter. The number of cases in which this procedure has been done is still small. It has been used only in those patients in whom an intractable dyskinesia of the sphincter was apparently the sole cause for the postcholecystectomy syndrome. Its use has not been extended to paralyze an ampullary sphincter in those cases in which either a biliary or pancreatic reflux had been proven. There were seven cases in which endocholedochal sphincterotomy was performed. Six of the cases have been followed, one for six years, one for five years, one for three years, two for eighteen months, and one for six months. All have shown definite improvement and have been relieved of their troublesome symptoms. Whether surgical section of the sphincter permanently destroys its action, and whether the resulting scar will cause a secondary contraction of the papilla with stenosis and biliary stasis, only careful

follow-up of these and other cases will reveal. To date, none of these anticipated theoretical complications have resulted. Many of the other involuntary sphincters of man, when divided, never again fully regain their function, and when healing takes place a stenosis does not result. Perhaps the sphincter of the common bile duct and the ampulla may be placed in a similar category.

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PARENTERAL FLUIDS AND FOOD IN GASTROINTESTINAL DISEASE*

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INTRODUCTION

THE use of parenteral fluids is so extensive at the present time and their value so widely recognized that it would seem superfluous to make it a subject for discussion except that one of my primary purposes is to include this procedure with a relatively new one which may be called the parenteral administration of food, or when the vein is used intravenous alimentation. Indeed, there is no particular reason why all such parenteral injections cannot be considered as food inasmuch as they all introduce nutritional elements and in so doing spare completely any activity on the part of the gastrointestinal tract. More important, however, is the fact that by including all of the nutritional elements in parenteral injections great advances can be made in the treatment of many gastrointestinal diseases.

Adequate parenteral food probably requires but five of the six nutritional elements. The sixth element, fat, is omitted even though there is considerable evidence that it supplies more than calories in the growing organism. It also is a vehicle for vitamins A and D. Nevertheless, for purposes of maintenance during parenteral nutrition for short periods it is probably not essential. The remaining five are the following: 1. Water, 2. Electrolyte, 3. Calories, 4. Protein, and 5. Vitamins.

Of these, the first three are commonly introduced in the usual injections of parenteral fluids, i.e., solutions of Ringer's and saline plus glucose. As to the fifth element, vitamins, many of them have become available in pure form and can be injected either intravenously or subcutaneously. These include vitamin C, thiamine, riboflavin, niacin and several others. However, I might emphasize that any discussion of nu-

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TABLE I

PARENTERAL FLUID AND FOOD: APPROXIMATE REQUIREMENTS AND DEFICITS

	Normal daily quota	*Loss*	*Total Deficit*
Water (in c.c.)	3,000	up to 10,000	10,000
Electrolyte (as NaCl- in gms.)	5 to 10	20	70
Protein (in plasma or as amino-acids- in gms.)	70	200	2,000 or more
Calories (as glucose- in gms.)	100*	—	—
Vitamins (see text)	—	—	—

* See text for justification of this figure.

trition whether enteral or parenteral must include consideration of all of the 5 elements listed above because it is quite probable that each requires the presence of the others to achieve adequate utilization. For example, carbohydrate metabolism is known to require the presence of at least thiamine and niacin; utilization of protein undoubtedly requires the presence of glucose; the behavior of protein is influenced by certain of the vitamins. Moreover, fluid and electrolyte balance is often impossible in the presence of severe hypoproteinemia, which commonly accompanies "salt edema." For these and other reasons, therefore, I shall approach the subject of parenteral fluids and food by taking into consideration all of the elements necessary for nutrition. Attention will be confined, however, to the nutritional requirements for maintenance but not for growth, irrespective of whether an adult or a child is under consideration. The reason is obvious; parenteral nutrition is always of limited duration and is used only when the gastrointestinal tract is temporarily out of commission, particularly when an abdominal operation is to be carried out.

Utilization of Parenteral Food: Any fluid or food introduced parenterally obviously reaches the lungs and the systemic tissues before it

reaches the liver, in contrast to absorption from the gastrointestinal tract, from which, of course, they first reach the liver. It is important, therefore, to know whether the parenteral route leads to any significant difference in utilization. The investigations along this line have not been extensive, but there is ample evidence in the case of glucose (provided the injection is not too rapid) that utilization is almost complete and that glycogen of the liver is increased following intravenous injections.[1] The same is true of electrolytes and also of vitamins, although renal excretion of the latter, particularly when given intravenously, does lead to considerable loss in the urine. With protein it has been shown that in the case of appropriate amino-acid mixtures similar results are found with nitrogen balance and serum protein regeneration whether the solution is given intravenously or by mouth.[2] Moreover, utilization of the protein in plasma transfusions has been demonstrated.[3] We may say with confidence, therefore, that the parenteral route permits satisfactory utilization of foods in spite of the fact that they do not first reach the liver.

Indications for Parenteral Food: Parenteral administration of fluids and food is indicated whenever the gastrointestinal tract cannot or should not be used, either completely or partially. Under such conditions failure to utilize the parenteral route will lead to deficiencies in one or more of the five elements listed above.

The first and most obvious indication for parenteral feeding includes patients unable to take any food or fluid by mouth because of vomiting, obstruction, etc. Second are patients in whom the utilization of food by mouth is incomplete or unsatisfactory, as, for example, patients with severe diarrhea or with intestinal fistula. Third are patients in whom oral ingestion of fluids or food is actually deleterious, such as those with peritonitis or other inflammatory disease, or those operated on, in whom complete rest of the gastrointestinal tract is important. Fourth is an ill-defined group in which for one reason or another, usually severe anorexia, the oral intake of fluid or food, while possible, is inadequate. While the intake of food may be increased in these patients by gavage feedings, such a procedure is often followed by vomiting or diarrhea. In this group of patients it may be extremely important to supplement the oral intake by parenteral injections. Fifth, parenteral administration of food may prove important where time is limited for correction of nutritional depletion. For example, in pre-

paring extremely malnourished patients for operation, the parenteral route may enable a nutritional deficit to be corrected even partially in a few days rather than in a few weeks, and this may greatly shorten the length of convalescence.

Daily Requirements Versus Deficits

The administration of parenteral fluids and food can be most effective only when a sufficient amount is given and retained; moreover, the rapidity of administration is often important. For these reasons it is essential to know rather definitely how much and how rapidly the various elements may be given. In arriving at these figures it is valuable to consider the daily requirements in contrast to the deficits present. Both are important, but the amounts are different with each of the various nutritional elements, which are therefore discussed separately.

Water: The daily requirements for water are, under ordinary conditions, about 3000 cc.; this covers about 2000 cc. in the expired air and perspiration as insensible losses and 1000 cc. to take care of urinary and fecal excretion. In high environmental temperatures the loss in the skin and lungs may reach many liters and this fact obviously increases the daily requirement. Many pathological conditions involving diarrhea and vomiting increase the daily requirement but these will be considered under deficits.

Deficits in water will accumulate whenever the daily requirement is not met by the daily intake. It is increased, of course, by abnormal losses such as diarrhea, vomiting, loss through fistulas, etc. Very rapidly, however, dehydration follows, and unless relieved, it will lead to the death of the individual. Although the exact figures are difficult to obtain, in the most dehydrated individual it is probable that a deficit up to 10,000 cc. may occur and that such a volume may be needed to restore fluid balance to normal. Because about 70 per cent of the body is water[4] one might expect deficits to be larger. However, the more active fluid compartments of the body comprise but 20 liters[5] which includes the plasma of the blood and the other interstitial (extracellular) fluid. Of these two compartments, the plasma amounts to but 3 liters. It is probable that not more than half of the extracellular fluid and very little of the intracellular fluid can be lost without serious results. Thus a serious water deficit would scarcely exceed about 10 liters and this should present no problem in correction inasmuch as the par-

enteral administration of this amount of fluid should easily be possible within 48 hours or less.

Electrolyte: There are many aspects of electrolyte behavior which it will be impossible to bring within the scope of this paper, as for example its influence on acid-base balance. However, with normal kidneys one may assume that variations in acid-base relationship produced by electrolyte loss can readily be adjusted by the adequate administration of solutions containing sodium chloride. If there is any reason to suspect that the renal function, even temporarily, is not normal, the compensatory mechanism may not operate and acidosis will remain uncorrected. In such an event it is very important that sodium lactate be substituted for saline or given as lactate-Ringer's solution. This will correct acidosis without action of the kidney and do so much more rapidly. Moreover, the lactate is an added source of glucose to which it is metabolized.[6] Sodium and potassium abnormalities will not be discussed inasmuch as we shall not be concerned with alterations in capillary or cell wall permeability. The discussion will be confined to the requirements of electrolyte under normal conditions in which sodium chloride or at most the salts present in Ringer's solution are sufficient.

Normally about 5 to 10 grams of sodium chloride are excreted in the urine and unless this is restored an electrolyte deficit will eventually result. Ordinarily, however, the body will first conserve salt in the absence of any intake by excreting very little in the urine. In most cases electrolyte deficiency is associated with water deficiency and the conditions leading to such deficits have already been described. On the other hand, examples of pure electrolyte deficiency occur in at least two conditions without an associated deficiency in water. In one case it is due to excessive perspiration in individuals taking sufficient pure water and is well known as heat cramps or heat exhaustion. The other instance is sometimes spoken of as water intoxication but is extremely rare; in this condition so much water without electrolyte is given that an acute mineral deficiency is produced.[7] Aside from these two instances, most patients with electrolyte deficiencies are also dehydrated and require water as well as salt.

The magnitude of electrolyte deficits has been well studied by many workers, including especially the well-known investigations of Coller and his associates.[8] By analyzing the chloride concentration of the plasma of patients who had lost large amounts of water containing

salt (e.g., gastrointestinal secretions by vomiting) they have calculated that for every drop of 100 mg. per cent in serum chloride the patient needs one-half gram of sodium chloride per kg. of body weight. In the case of an adult weighing 70 kg. who shows a drop in the chloride of 200 mg. per cent (a severe deficit), as much as 70 grams of salt would be required for its correction. In terms of physiological saline this would amount to nearly 7 liters. Thus it is obvious that even the correction of such a severe electrolyte deficit is neither difficult nor should it require more than 24 to 48 hours.

Vitamins: Only one of the many vitamins will be discussed because most is known thereof. Vitamin C may be removed from an otherwise complete diet, yet months are required before evidence of scurvy develops. Nevertheless, it is now known that even a severe deficit can be rapidly corrected by the injection of a gram of the vitamin per day for but a few days.[9] A similar and perhaps just as easy solution probably exists with the other vitamins now available for parenteral administration.

Calories: An adult of average size at rest in bed is said to require 1600 calories per day, which means, of course, that if no caloriogenic food is ingested he will obtain these calories from body tissue. The glycogen would be depleted within a day or two, and thereafter calories would originate entirely from protein and fat tissue. Inasmuch as the protein tissue may be considered as essential and the fat tissue as unessential, it is of great importance to determine to what extent we may depend upon fat tissue to supply calories in a patient unable to take any food by mouth. A rough approximation may be obtained from data acquired during the course of complete versus protein starvation. After several days of complete fasting 15 grams of nitrogen appears in the urine,[10] whereas only 5 grams are found when sufficient glucose and fat are supplied to meet the caloric needs. Thus we may assume that the difference of 10 grams represents the amount of protein tissue broken down under conditions of complete starvation to supply glucose for energy requirements. Ten grams of nitrogen represent 62.5 grams of protein or about 250 calories. This means that under complete starvation but one-sixth of the energy requirements are supplied by protein tissue; it may be assumed that the rest is supplied by tissue fat. This is an important calculation inasmuch as it relieves much of the responsibility of supplying full energy requirements in parenteral

injections. If tissue fat may be counted on to supply even three-fourths of the caloric requirements, the problem of administering enough glucose becomes simplified. Thus in an average sized adult 100 grams of glucose per day should be adequate and with the metabolism of enough tissue fat should enable the body to meet the energy requirements without the necessity of using tissue protein.

Protein: Parenteral protein alimentation has been achieved only recently. For a long time no attention was paid to protein intake because it was assumed that such large stores exist that a person could live in health for months or even a year with no protein at all provided merely that his energy needs were met. It is true, of course, that muscle tissue, containing 20 per cent by weight of good protein, forms a large part of the body mass and that it may even be considered as non-essential and therefore a theoretically excellent store of available protein. Moreover, it has been assumed that perhaps a kilogram or two of "deposit" protein is readily available, enough to last for at least several days. The difficulty is that there is no selective depletion of either muscle or "deposit" protein. Much evidence has been accumulated to show that plasma and liver protein as well as muscle is depleted whenever there is an insufficient protein intake.[11, 12] In other words, we cannot assume that protein intake is unimportant. It may be even more important than water and electrolyte and vitamins. Certainly protein is an essential ingredient of protoplasm and is vital to all life processes.

The daily requirement of protein under normal conditions is fairly well established at about 1 gram per kilogram of body weight. This assumes, of course, the inclusion of enough protein, containing a sufficient proportion of all the essential amino-acids. Such an intake would insure against protein depletion except under certain abnormal circumstances during which excessive amounts of protein tissue are broken down. Fever, trauma, infection cause excessive protein tissue breakdown and may require the daily intake of two or three times the normal amount of protein per day to keep the body in protein, often called nitrogen, balance.

Deficits in protein are most interesting and important inasmuch as they become quite large, are difficult to correct, and require long periods of time, unlike water, electrolyte and vitamin deficits, which are easy to correct. The magnitude of the protein deficit is, of course, increased by the use of protein to supply energy whenever

caloric intake is insufficient. Whereas about 30 grams per day will meet the normal protein tissue breakdown when energy requirements are met, as much as 100 grams may be needed when no energy comes from other food. Moreover, this loss is cumulative. Once protein tissue is lost it cannot be replaced by any other food element. Fat and carbohydrate are both available for energy and the latter is transferable to the former under appropriate circumstances; but except for plants and ruminants, protein requires protein for replacement.

During complete starvation, though adequate water and electrolyte are supplied, a 100 gram loss of protein will in 20 days amount to 2000 grams; in 30 days to 3000 grams. Thus in a severely depleted patient the amount of protein lost will reach a large figure. But the problem becomes greater when one realizes how difficult it is to correct such a deficit rapidly. In the example just cited it would take the patient just as long to correct his depletion as it did to produce it, provided he could ingest 100 grams of protein a day, which in itself may be impossible in the presence of anorexia or other factors preventing or limiting oral feeding. The time factor must also be considered. If one wished to correct a vitamin C deficiency of six months duration in three days one needs only to inject a gram a day of the crystalline vitamin. But can a protein deficit of 2000 grams be corrected in two days by giving 1000 grams a day? This question is merely asked to focus attention on the practical side of meeting severe protein deficits rapidly.

In practice, of course, it is, in all likelihood, not necessary to meet protein deficits completely any more than it is necessary to correct vitamin deficits completely. Nevertheless, the aim should still be to determine how large an intake is possible in order to correct the protein deficit as completely and in as short a time as possible.

Amino-acids as Parenteral Protein Food

The injection of ordinary food protein directly into the blood stream is dangerous in view of the anaphylactic effect of parenterally introduced foreign proteins. An exception to this rule is the apparently relative safety with which solutions of gelatin may be injected intravenously. However, little is known of the metabolic behavior of solutions of gelatin. Moreover, this protein lacks essential amino-acids so that it can scarcely be considered an adequate source of protein food.

At the present time, therefore, human plasma and amino-acid mix-

tures are the only two methods of introducing protein nourishment parenterally. Experience with each of these methods is not very extensive, dating back only about 5 years or so. However, a good deal of information has been accumulated and a few of the pertinent facts may be cited.

Plasma Versus Amino-acids as Parenteral Protein Food: Plasma as a source of protein food has the following *disadvantages:* 1. It is inconvenient and expensive inasmuch as one liter of plasma contains but 60 grams of protein and requires 4 donors besides the processing necessary before it can be used. 2. One liter of citrated plasma contains five grams or more of sodium citrate which under certain circumstances may prove deleterious. 3. It is likely that plasma protein must be metabolized into smaller units before the protein can be utilized by other tissues of the body. 4. It is probable that plasma protein is not a complete protein lacking sufficient arginine and isoleucine.[13] On the other hand, plasma contains proteins which are apparently utilized by body tissue; however, the great *advantages* of plasma are largely due to the fact that it supplies protein immediately to the circulating blood and thus is of tremendous value in critical cases of hypoproteinemia in which the correction of this deficit is urgently needed.

In contrast to plasma, amino-acids have certain advantages. 1. Amino-acid mixtures as a method of parenteral protein food are much more physiological inasmuch as amino-acids are the form in which protein nourishment normally enters the body. The injection of such mixtures, therefore, is in reality a physiological shortcut, i.e., it supplies protein nutrition without any activity on the part of the gastrointestinal tract whatever. Thus the injection of such mixtures supplies the building stones for the correction of deficits throughout the body. It must be admitted, of course, that synthesis of protein from amino-acids requires appropriate enzymes and hormones and that these may be lacking in certain cases. However, it is probable that when they are present protein synthesis is rapid. 2. Another advantage of amino-acid mixtures over plasma is the relative simplicity and economy with which they may be given; as available at the present time solutions of amino-acids and polypeptides can be injected along with glucose and saline and their cost is not much greater than solutions containing glucose and saline alone.

Protein Hydrolysate as a Source of Amino-acids: While pure crys-

talline amino-acids in appropriate mixtures are available and offer many advantages, the cost of such a preparation is still so great as to make them prohibitive for general use. However, appropriate mixtures of amino-acids and small peptides can be produced by digestion of proteins which have been so purified as to permit their injection with complete safety even in large amounts. The author has used such a preparation which is called Amigen,* an enzymic hydrolysate of casein and pork pancreas and which contains a mixture of amino-acids and peptides in the proportion of 70 to 30. This particular hydrolysate contains all the essential amino-acids as shown by the fact that it supports normal growth in rats when supplied as the only source of nitrogen nourishment.[14] It has also been shown to lead to positive nitrogen balance as well as to satisfactory evidence of serum albumin regeneration both in humans and in animals.[2, 15]

As available at the present time, Amigen solution is adjusted to a pH of 6.5 by the addition of sodium hydroxide so that each liter of 5 per cent Amigen contains about 5 grams of sodium chloride. Amigen exerts about the same osmotic pressure as an equivalent amount of glucose, its particle size in solution averaging a molecular weight of about 130. As used by the present author a liter of solution containing 50 grams of Amigen and 50 grams of glucose is injected, thus furnishing the patient 4 of the 5 nutritional elements, i.e., 1000 cc. of water, 5 grams of sodium chloride, 50 grams of glucose and 50 grams of protein.

Untoward Reactions: The administration of parenteral protein food in the form of Amigen solution has been fairly extensive and the procedure has passed well beyond the experimental stage. It is probable that thousands of patients have received this form of intravenous feedings; the present author has used it in hundreds of cases. It is true that untoward reactions have been observed following the injection of Amigen solutions, but such a statement can also be made of blood transfusions and in fact of most intravenous injections. The important point is that such injections of Amigen solution have been made in a sufficiently large number of patients to warrant the statement that such a procedure is entirely safe provided the usual precautions are taken for intravenous injections and particularly that the injections be given slowly enough. One liter of 5 per cent Amigen solution contains 50

* Manufactured by the Mead Johnson Company of Evansville, Indiana.

grams of protein nourishment, which is a fairly large protein intake. To introduce such an amount in less than an hour is very apt to provoke nausea, abdominal pain, vomiting, as well as flushing of the skin and a chilly sensation, the nature of which is not entirely understood, although similar reactions have been observed with mixtures of pure crystalline amino-acids made up to match as closely as possible the amino-acid composition of Amigen. From these observations it is fair to infer that such reactions are not due to impurities but are part and parcel of the effect produced by amino-acids themselves when introduced directly into the circulation at too rapid a rate, a phenomenon which probably never occurs under normal absorption from the gastrointestinal tract. In actual practice the speed of injection tolerated without symptoms varies greatly from patient to patient. In coöperative, intelligent individuals the rate of flow is left to the patient himself by placing the regulatory screw clamp within his reach.

True pyrogenic reactions, i.e., chills and fever, have also been observed, but in such instances it has been the experience of the present author that causes other than the amino-acids have been responsible. For example, in the desire to inject Amigen solutions slowly the rate of flow is often cut down so much that the fluid may stop for short periods of time, permitting a reflux of blood into the shank of the needle. Such blood may easily clot and particles of it may enter the circulation when the flow is restarted or increased; under such circumstances, a pyrogenic reaction may readily occur. Contaminated solutions, of course, will obviously produce pyrogenic reactions, and great care must be exerted as with blood and plasma to avoid such contamination. Recently at the Barnes Hospital 200 consecutive liters of 5 per cent Amigen and 5 per cent glucose solution have been injected intravenously into 15 patients with no pyrogenic reactions whatever. In this group the greatest amount given to one patient was 26 liters. Actually our percentage of reactions with Amigen is less than with citrated blood.

Phlebitis: The occurrence of phlebitis following the intravenous injection of Amigen has been observed, but so has phlebitis been encountered with the intravenous injection of other solutions, particularly those which were hypertonic. In the experience of the present author the injection of a solution containing 5 per cent Amigen and 5 per cent glucose produces no more phlebitis than a 10 per cent solution of glucose. It is obvious, of course, that if this solution is diluted with

distilled water the tendency toward phlebitis will be much less. The disadvantage of this, however, is that a larger amount of water is injected than is necessary; conversely, less nourishment can be given from the same volume of fluid.

Subcutaneous Injection of Amigen: The injection of Amigen subcutaneously is preferred by some and the present author has also used this method. It is necessary, of course, to prepare a mixture which is not hypertonic. Ordinarily the dilution of the above mentioned solution containing 5 per cent Amigen and 5 per cent glucose with an equal quantity of pure water permits satisfactory injection of the solution under the skin. At the St. Louis Children's Hospital the subcutaneous solution is prepared by adding equal parts of 10 per cent Amigen, 10 per cent glucose and normal lactate Ringer's solution. Here again the disadvantage of this method of administration is the relatively large volume of fluid which must be given.

Calculation of the Daily Parenteral Diet

If the patient is clearly dehydrated, it will be necessary at the very outset to inject as much as 5 to 10 liters of normal saline or Ringer's solution to correct the water and electrolyte deficiency. In addition to this, a plasma transfusion of a liter or more may be required to correct an acute hypoproteinemia, particularly when any evidence of circulatory impairment is present or imminent. After these more or less acute requirements have been met, it is probable that the daily amount of parenteral food may be cut down considerably as follows.

For the adult of average weight with a moderate protein deficit, 3 liters of fluid are given each day, of which 1 liter is Amigen solution containing 5 per cent each of Amigen and glucose, the other 2 liters being 5 per cent glucose. Thus in these 3 liters of fluid the patient receives the following nutritional intake:

Water	3000 cc.
Electrolyte	5 grams
Glucose	150 grams
Protein	50 grams

The above intake is used ordinarily although in depleted patients one liter of glucose may be replaced by a second liter of Amigen, thus increasing the protein intake from 50 to 100 grams. In more severely

depleted cases, the amount of fluid may be increased to 4000 cc. by the addition of another liter of Amigen and glucose solution. Thus the patient would receive the following:

Water	4000 cc.
Electrolyte	15 grams
Glucose	200 grams
Protein	150 grams

In still more severely depleted patients, it may be possible to increase the intake of protein even more in view of evidence indicating[16] that as much as 10 grams of protein per kilo per day can be metabolized. However, clinical experience with the larger amounts of Amigen are still limited; the most the present author has injected has been 300 grams of Amigen and 300 grams of glucose in 24 hours for 3 consecutive days in 2 patients by a continuous venoclysis of 6 liters per day. The injections were well tolerated with evident clinical improvement.

Separately the following parenteral mixture of vitamins may be injected for the daily requirement. Much more will be necessary if a depletion is present or suspected. (The doses listed are approximate and are partly based on the now available preparations which also offer widely variable mixtures. Vitamins C and K, however, are always given individually. Not listed are inositol and choline as well as the fat soluble vitamins which are also available and may be given intravenously, intramuscularly or subcutaneously. Various liver extracts containing vitamins and probably other important elements are also often given parenterally.)

Vitamin C	100 mg.
Thiamine	5 mg.
Riboflavin	2 mg.
Pantothenic Acid	4 mg.
Pyridoxine	2 mg.
Niacin	20 mg.
Vitamin K	10 mg. (as needed)

Results of Parenteral Feeding in Gastrointestinal Disease

That food is essential for normal resistance to disease should require no proof. Yet it is remarkable how often this fact is overlooked and how frequently we rely on reserves of nutritive elements which

may or may not be present or may have been depleted before operation is carried out. It might be well to cite the striking observations made in this city by Mulholland, Co Tui and their coworkers[17] on the beneficial effects which followed prompt postoperative administration of a large amount of food including protein by utilizing a jejunal tube for alimentation. The important point is that food is just as essential whether the administration can be oral or must be parenteral. Nevertheless, the parenteral administration of food has for decades been confined to water, electrolyte and glucose with the addition of several of the vitamins within the past few years. While correction of dehydration with such fluid has reduced mortality and extended the field of surgery tremendously, still further advances will be made possible by applying knowledge of nutrition, particularly of protein, to parenteral administration in patients unable to take any food by mouth. While the administration of an absolutely complete* parenteral diet has not as yet been achieved, the addition of protein nourishment as amino-acids to parenteral fluid has been of decisive significance. Such a parenteral diet has been given to hundreds of patients and the results have been published by a number of observers.[15,18,19]

Permits Rest Without Starvation in Non-surgical Diseases: In many patients with non-surgical diseases of the gastrointestinal tract, malnutrition is inevitable because a sufficient amount of food cannot be ingested or assimilated. In many instances the physician wishes to put the gastrointestinal tract completely at rest so that this important principle may be utilized. Yet by so doing the malnutrition already present is aggravated. Only by feeding the patient parenterally can the principle of rest be carried out without starvation. Indeed, healing is so dependent on the presence of adequate nutrition that rest of the gastrointestinal tract often defeats its purpose because it increases the degree of malnutrition.

Thus the use of parenteral food in non-surgical diseases is logical and should prove extremely beneficial although few cases have been so treated and the actual results cannot be described. The present author has little occasion to treat such patients, e.g., ulcerative colitis, but he has observed two children in whom a prompt remission of the severe

* Missing is fat and several vitamins. It is not known how serious this is in patients ordinarily treated by parenteral injections. It is probable that for them the elements now available do actually comprise a complete diet. It must be admitted, however, that further research will show the indispensibility of certain elements whose importance is now obscure or unknown.

diarrhea followed complete rest of the gastrointestinal tract (aside from the ingestion of tablets of sulfasuxidine) with the administration of a complete intravenous or subcutaneous diet.

Extends the Indications for Surgery: Extensive gastrointestinal surgery, particularly the removal of carcinoma, imposes a great risk, especially when the patient is malnourished and depleted to begin with. The long and tedious procedures necessary to remove all cancerous tissue has in the past denied many individuals any hope of surgical cure. That adequate preparation before operation will enable much more extensive procedures to be carried out safely is widely known. But such preparation is much more complete when all the elements of the diet, particularly protein, have been included. It has been the experience of the author and of other surgeons as well, that when a patient has received adequate parenteral injections of the 5 nutritional elements described for a week or more, extensive surgical procedures could be more safely carried out with much less tendency toward shock during and immediately after operation. This is particularly true of older patients many of whom suffer various types of malnutrition particularly hypoproteinemia.[20]

This method of therapy is still relatively new and actual figures of mortality cannot be cited because the amount of experience is not great. It is quite probable, however, that with the use of this new method of preparation the boundaries of gastrointestinal surgery can be greatly increased because much more extensive procedures will become possible with relative safety.

Facilitates Surgical Procedures: Many patients with long-standing diseases of the stomach or intestines particularly those who have had symptoms of obstruction will present at operation an edema of the stomach or intestinal wall which is partly inflammatory but is often partly nutritional. Much of the edema and even distention will subside on complete rest of the gastrointestinal tract as well as efficient gastrointestinal decompression. If to these measures the surgeon will add the administration of an adequate amount of parenteral food the return of the stomach and intestines to a normal healthy condition will be more complete. It has been impressive to note the collapsed thin-walled condition of the gastrointestinal tract in such patients after a week of such preoperative preparation. The technical procedures which have to be carried out are much easier and healing is much more rapid and sure.

Minimizes Postoperative Complications: Here again it should require no detailed evidence to prove that adequate nutrition will enable more perfect and rapid healing. Complications which follow gastrointestinal diseases are to a large measure due to the effects of partial or complete starvation. These inevitable nutritional deficits are aggravated by actual loss from vomiting, diarrhea or exudation from the extensive surfaces of the peritoneal cavity or into the wall of the gastrointestinal tract. Physicians and surgeons alike have not hesitated to put the gastrointestinal tract at rest and have combated the effects of the resultant starvation at least partially by supplying water, electrolyte, glucose and some vitamins. Only recently, however, has the addition of protein made this parenteral diet more complete. Yet it is the protein deficit which is largely responsible for most of the complications. There is an increasing realization that hypoproteinemia, for example, is frequent and associated with many of the difficulties which follow surgery.

An Ounce of Prevention Is Worth a Pound of Cure: After the introduction of amino-acid mixtures several years ago their injection as a means of supplying parenteral protein food was used only in severely depleted individuals who developed difficulties after operation, usually associated with hypoproteinemia. Under these circumstances the protein deficit is great and the correction difficult, requiring many days. On the other hand, if the surgeon realizes that protein deficits are cumulative and inevitable, he will begin to supply protein parenterally from the very moment protein nourishment is withdrawn from the diet; in other words, he will make his parenteral injections fulfill the requirements of a complete diet and thus prevent many clinical manifestations which follow protein starvation. The present author now often includes Amigen solution as routine after any abdominal operation even though the patient is in perfect health at the time of the operation. If glucose is added to the parenteral injections after operation to supply calories, protein nourishment is also added. Indeed, protein is probably more important than calories, inasmuch as the latter can be supplied if necessary from body stores of glycogen, tissue fat and tissue protein. On the other hand, there is no substitute for tissue protein and, unless supplied in the diet as such or as an adequate mixture of amino-acids, depletion is inevitable.

(SEE NEXT PAGE FOR REFERENCES)

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NUTRITION IN MEDICINE*

The Wesley M. Carpenter Lecture

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NUTRITION is the science of food and its relation to health, and as such it is inseparable from any concept of medicine. Throughout the history and development of medicine, food and nourishment have always been considered as important environmental factors in health, and in the treatment of disease—particularly in convalescence. Current concepts of nutrition are really the result of 20th century developments in chemistry and physiology, and as all of us are aware, the last decade or so has witnessed remarkable advances in nutrition, both in fundamental nutrition and in the application of nutritional information to the diagnosis and treatment of disease and in the broader field of improved health.

This emphasis on relatively recent advances in nutrition does not mean, that as a whole we are today any better fed than we were 100 years ago—for whenever man has consumed food in such variety and quantity that all bodily needs are fully met, he has been well nourished. But these more recent advances in nutrition do permit us to define good nutrition more clearly, and to use available nutritional information more effectively. Unfortunately there have been many overenthusiastic and misleading statements regarding the value of certain nutrients in the treatment of specific diseases, and to health in general. I refer specifically to the vitamin field. There also have been many misleading statements regarding the prevalence of malnutrition in this country. These unsubstantiated claims have had two unfortunate results: they have not encouraged the vast majority of competent medical men to have a real appreciation of good, sound nutrition; and they have opened up a "vitamin racket" rivaling that of the patent medicine days. It is as important that we learn the things that good nutrition cannot do, as it is to learn what it can do.

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The invitation to make this address requested that it include comments on nutritional requirements for man, vitamin therapy, and use and abuse of vitamins in nutrition. After remarks on these points, I wish to comment on recent views concerning the prevalence of malnutrition in this country, and then to mention briefly certain classic experiments which emphasize the importance of superior nutrition to health. Finally, I should like to suggest certain positive measures whereby nutrition may come to be of greater value to medicine.

The nutritional requirements for good health consist of adequate quantities of protein, fat, carbohydrate, certain minerals, certain vitamins, and water. Under ordinary conditions, and even today in this country, the normal individual can obtain adequate amounts of these nutrients from food. In fact, adequate nutrition for man over any length of time can be obtained only by consuming foods in such quantity and variety that nutritional needs are fulfilled. Man relies principally on appetite and on variety in the choice of foods to secure a balanced diet. Variety in the choice of foods is affected by food habits, purchasing power, and availability of food. Probably the simplest principle for the normal individual to follow in attaining good nutrition is to consume a wide variety of foods that have undergone a minimum of processing, and let the appetite be the judge of quantity consumed. One can improve this principle by knowing something of the nutritional requirements of man and how they are fulfilled by various foods, for one can then select those combinations of foods which will furnish in adequate quantity the various ingredients now known to be necessary for good nutrition. But with the ill individual one should not rely on appetite as a stimulus for adequate food intake, for anorexia may be part of the symptom complex.

It is important to remember that there are no absolute requirements known for any food factors. All the requirements we speak of are relative requirements. For example, the amount of protein we need depends in part on the amount of fat and carbohydrate in the diet, the amount of thiamine we need depends on the amount of carbohydrate and fat in the diet, the amount of riboflavin and niacin we need may depend on the amount of protein in the diet, and so forth. There are many complicated and dynamic interrelations in intermediary metabolism, and so when we speak of nutritional requirements we usually refer to an average person on an average diet. The figures given are usually

optimal, as they should be for optimum health, sufficiently high to allow a generous margin of safety for individual differences in requirements, and to cover any errors in our knowledge of nutrition.

Protein is the principal nitrogenous constituent of animal and vegetable tissue. In the process of digestion, the large protein molecules are broken down into units that are simpler from a chemical viewpoint, and ultimately into small molecules, the amino acids. There are about twenty-four known amino acids; of these somewhat less than a half are the so-called essential amino acids. This means only that our body tissues cannot make these amino acids, that we must receive them ready made from our food. The other amino acids play a part in metabolism, but presumably they can be synthesized in the body and hence it is not essential that they be obtained from food. Protein nutrition is thought of today in terms of essential amino acids, but we lack information on the amounts and kinds of amino acids in foods, and on the qualitative and quantitative requirements of man for amino acids, so one still speaks of protein requirement. For the average normal adult, a protein intake of 1 gram per kilogram of body weight per day is sufficient. About one and a half times as much is desirable for the pregnant woman and two or two and a half times as much for the lactating woman or the actively growing child. Most of us obtain protein from both animal and vegetable sources, and generally speaking, those proteins of animal origin which include not only meat but milk, eggs, fish, and fowl are of higher biologic value than vegetable proteins, because they contain more of certain of the essential amino acids. But vegetable proteins supply many of the essential amino acids, and other amino acids, as do animal proteins, which are also used by the body. Some vegetable proteins such as those of yeasts, peanuts, soybeans, and various seed germs are good quality protein.

Thus for the protein allowance, let us use the common figure of 1 gram per kilogram body weight per day, or 70 grams for an average man, and receive some of it from animal and some from vegetable sources. One cannot be too dogmatic about the proportions of animal and vegetable protein, nor about the absolute amount of protein. Recent investigations[1] with man have shown that as little as 50 grams of protein, of which not more than 5 grams were animal protein, were sufficient to maintain good health in hard working, healthy young adults over a two month period. But may I emphasize that the diet used in

these investigations was excellent in all other nutrients and provided adequate calories, and that 50 or 70 grams of protein is not the same as 50 or 70 grams of protein food. In terms of protein foods these values would be three to five times more because of the water content of the food. May I further stress that these subjects were healthy young adults, not growing adolescents or pregnant or lactating women.

Fats are the most potent sources of energy we have. Another important function is that they serve as carriers for the fat soluble vitamins. Experimentally, it has been shown that certain unsaturated fatty acids are essential to the rat, but it is not known whether man needs these unsaturated fatty acids. At any rate it is most unlikely that our diets would ever be deficient in these substances. In our diet, fat is obtained from both animal and vegetable sources. Hydrogenated cottonseed oil is the basis of various substitutes for natural fats. Margarines are made from animal and vegetable fats. When vitamin A is added to margarine, it is as nutritious as butter in mixed diets for man.

Actual fat intake is influenced considerably by food habits. Generally fat furnishes from a fourth to a third of the daily caloric intake, which would mean that we consume around 100 grams of fat per day. But one can get along with less fat if sufficient carbohydrate is available for energy needs and if there are adequate sources of vitamin A available. This is usually possible because the body can synthesize vitamin A from the yellow pigment carotene which is present in most green and yellow vegetables. More fat is desirable in hard manual labor because of the increased caloric needs, which cannot be satisfactorily fulfilled by the more bulky carbohydrate foods.

Carbohydrate is plentiful in our diets. As with fat, the requirements for carbohydrate depend on activity, and actual intakes are graded largely on food habits. Because of its relatively low cost, and the ease with which it can be obtained, large amounts are consumed. A sedentary person may consume from 150 to 200 grams of carbohydrate per day, whereas an active person may consume three to four times that amount.

Certain inorganic or mineral elements are just as necessary to our health as are other nutrients. Experimentally with the rat it has been shown that some 12 minerals are necessary for good nutrition, but many of these are necessary only in minute amounts. Undoubtedly man also requires many of these minerals, but from the practical view we need consider only a few. Sodium and chlorine are needed in relatively

large amounts and are easily supplied by the use of ordinary salt. The inorganic elements in which our diets are most likely to be deficient are calcium and iron, and in the inland areas iodine should be considered.

Milk and cheese are the only rich sources of calcium in the diet, though small amounts are obtained from most vegetables and fruits. Meats are a poor source of calcium as also are eggs. The calcium requirement for adults is a much disputed question. There are some who believe that 0.1 to 0.2 gram per day is sufficient, and others who feel that 0.7 to 0.8 gram per day is desirable. Until better factual information is available, it might be well to adopt a middle of the road policy, or 0.5 gram which is approximately the amount of calcium furnished in a pint of milk.

Iron is furnished by meat, generously by liver. Other good sources are eggs, leafy green vegetables, potatoes, dried fruits, and whole grain cereals. The iron in foods is not completely available to the body but on the average, 60 to 70 per cent is available. An average intake of 10 to 12 mg. of iron per day will satisfactorily fulfill the normal adult's requirement for this nutrient.

Iodine is needed only in small amounts, probably of the order of 0.2 mg. per day, and is adequately furnished by the use of iodized salt.

There are four fat soluble vitamins, and of these only vitamins A and D are of practical importance in the normal nutrition of man. The best sources of vitamin A are liver, egg yolk, whole milk, cream, and butter or enriched margarine. We can also utilize a substance from dark green leafy vegetables and from yellow vegetables, the pigment carotene, which in the body is converted into vitamin A. Another factor in our favor is that we have the capacity of storing, particularly in the liver and kidney, rather goodly amounts of vitamin A. Thus in the summer when an abundance of fresh vegetables is available, we may store vitamin A to help us through the winter.

The recommended daily dietary allowance of vitamin A for adults is 5000 I.U. per day. This amount of vitamin A is readily obtained from an intelligent selection of food, particularly if a serving of a dark green leafy or yellow vegetable is included daily. Lettuce is not a dark green leafy vegetable, particularly iceberg lettuce.

Concerning vitamin D, little is known about the requirement of adult man, but it undoubtedly is small. Few foods contain an appreci-

able amount of vitamin D. For it we depend principally on sunshine, except in infants and children where fortified milk may be used and where it is strongly advisable to use a fish liver oil or other rich source of this vitamin.

There are some 15 water soluble vitamins that have been described in experimental nutrition. Of these only four are of importance, as far as is known today, in practical human nutrition. These are ascorbic acid and three members of the vitamin B-complex–thiamine, riboflavin, and niacin. It is important to know that we do not have the ability to store the water soluble vitamins for any length of time as is the case with the fat soluble vitamins. Thus we must provide them in our diet regularly.

Ascorbic acid is obtained principally from citrus fruits, from tomatoes, or from raw cabbage. It is also obtained from salad greens, other fruits such as strawberries, peaches, and melons, and from potatoes when cooked in the skin. It is well to remember that ascorbic acid is readily destroyed by contact with air, particularly at an elevated temperature. The recommended dietary allowance for ascorbic acid is about 50 to 75 mg. per day which is the amount furnished by the juice of one large orange or contained in two glasses of tomato juice.

The vitamins of the B-complex are obtained chiefly from the protein foods and from the whole grains. Thiamine is present in large quantities in pork and liver and in good amounts in legumes, egg yolk, nuts, and whole grains or enriched flours. There is much riboflavin in milk and liver, and fair amounts in legumes and whole grains. Niacin is present in generous amounts in liver and other meat and also in whole grains and enriched flour; it is low in milk. The recommended daily allowances for the average adult for these three vitamins as given by the Food and Nutrition Board of the National Research Council are 1.8 mg. for thiamine, 2.7 mg. for riboflavin, and 18 mg. for niacin. It is quite probable that the figure for riboflavin–that is, 2.7 mg. per day –is high, and that a value of 2.0 mg. per day is a more reasonable recommendation.

Summarizing the available information on nutritional requirements for the adult, one could say that calories are required in an amount sufficient to maintain or adjust weight to a desirable level. Fat and carbohydrate are used principally for this purpose. Protein is recommended at a level of 1 gram per kilogram of body weight per day.

Minerals are adequately supplied by the use of meat or fish and vegetables, a reasonable amount of milk and cheese, and the use of iodized table salt. Vitamin A is the only fat soluble vitamin with which we need be concerned in normal adults. It is provided well through the use of egg yolk, liver, butter, enriched margarine, whole milk, tomatoes, and green or yellow vegetables. Of the water soluble vitamins, ascorbic acid is adequately provided by the daily use of citrus fruit, tomatoes, or raw cabbage. Thiamine, riboflavin, and niacin are well supplied by the protein foods particularly if some milk and whole grain or enriched cereals are included. As far as is known today, other nutrients still largely in the investigative stage, so far as they are required by man, are probably furnished in satisfactory amounts by the intelligent selection of good wholesome food.

The use of specific vitamins or vitamin mixtures in medical treatment should be based, it seems to me, on the best available information on what is considered to be the body requirements. It is impossible to give specific details of treatment, for like all other therapy it should be planned for each specific case. Unless there are conditions which prevent the normal ingestion or assimilation of food, an early and important therapeutic procedure is to make sure the person consumes a really good diet, so that he actually receives good nutrition. If the history, or clinical or laboratory findings suggest specific vitamin deficiencies, supplemental therapy, either orally or parenterally, as the situation suggests, is desirable. The following are useful ranges of specific vitamin dosages:

Vitamin A	Preventive Treatment – 2,000 to 5,000 I.U. per day Therapeutic Treatment–10,000 to 30,000 I.U. per day
Ascorbic Acid	Preventive Treatment – 25 to 50 mg. per day Therapeutic Treatment–100 to 300 mg. per day
Thiamine	Preventive Treatment –1 to 3 mg. per day Therapeutic Treatment–3 to 10 mg. per day
Riboflavin	Preventive Treatment –1 to 3 mg. per day Therapeutic Treatment–3 to 10 mg. per day
Niacin	Preventive Treatment – 5 to 20 mg. per day Therapeutic Treatment–50 to 300 mg. per day; when using these amounts, niacinamide is preferable.

We have found it convenient in preventive treatment in outpatient work and on the ward, to use an elixir of the water soluble vitamins made up so that 4 ml. or 1 teaspoonful contains 1 mg. of thiamine, 1 mg. of riboflavin, 10 mg. of niacin, and 25 mg. of ascorbic acid. This is inexpensive and convenient to prepare. At a dosage preferably of 4 ml. twice a day, it is entirely adequate for preventive treatment and can be well used in conjunction with therapeutic treatment.

Dried yeast is a convenient, effective, and inexpensive material to use in nutritional therapy. It furnishes not only vitamins of the B-complex, but also good quality protein, and when used in generous amounts it also contributes appreciably to the total protein, as dried yeast averages 40 to 45 per cent protein. But to administer effective amounts of yeast in preventive or therapeutic treatment, it is almost necessary to dispense it in bulk. Yeast tablets simply do not furnish enough yeast, even if one is willing to take ten to fifteen tablets a day. The average yeast tablet contains a little less than a half-gram of yeast so that even ten tablets per day would furnish not more than 5 grams of yeast. We have found it successful in preventive treatment to dispense 15 grams of dried yeast per day—with brewers' yeast this amounts to about one heaping tablespoonful—and to use two to three times this amount in therapeutic treatment. Only rarely do we find individuals who have gastrointestinal distress following ingestion of this quantity of dried yeast when it is divided into two or three doses per day. It is conveniently given in cold tomato juice. In fact a six or eight ounce glass of tomato juice with one or two heaping tablespoons of dried yeast is about the most effective and inexpensive type of generally good nutritional therapy. It furnishes significant amounts of vitamins A and C as well as vitamins of the B-complex and good quality protein. It is really nutritional therapy, not vitamin therapy.

It is well to consider therapy with the water soluble vitamins whenever parenteral fluids, particularly glucose, are given. Patients receiving parenteral fluids are usually not consuming adequate diets and since the water soluble vitamins are not stored in body tissues for any length of time, it is advisable to give them along with parenteral fluids. Recently there have appeared on the market convenient preparations of some of the B-complex vitamins in a form suitable for intramuscular injection, or for addition directly to the infusion material. I know of

none of these preparations which also contains ascorbic acid, but ascorbic acid should be included along with thiamine, riboflavin, and niacin in conjunction with parenteral fluids.

The use and abuse of vitamins simmers down to whether there is any need for them in the specific case in question. It is not an abuse to use them in investigative medicine or in any condition where there is any reasonable evidence or belief that they have been received in insufficient amount, and that their addition will be helpful. But it is not proper to publish premature and enthusiastic announcements regarding therapeutic findings. So frequently these are based on only a few cases with no adequate controls. This is most unfortunate because it arouses false enthusiasm and furnishes ideal material for exploiting the public. When these claims are tried and found wanting, one tends to be skeptical of other nutritional information which is really sound. As examples of unfortunate and extravagant claims one may mention the use of large amounts of vitamin A in the treatment of hypertension, of vitamin B_6 or pyridoxine in the treatment of Parkinson's syndrome, of thiamine in the relief of pain following dental extraction, of vitamin K in the prevention of dental caries, of calcium pantothenate or para aminobenzoic acid to restore gray hair to its natural color, and of pyridoxine in the treatment of acne vulgaris.

Probably the public is the greatest abuser of vitamin preparations, but the public is not solely at fault. It has been bombarded with misleading advertising and led to believe that a half to two thirds of our entire population is malnourished, and that if one is weak, tired, and fatigues readily, it is probably because he is one of the two thirds of the population that is not properly nourished. That may be the case, but it also may not be so. The result, unfortunately, is a tremendous misuse of valuable and expensive material. In most cases a more intelligent approach would be to improve one's selection of food—that is, if nutrition is at fault.

Many vitamin preparations now on the market contain small amounts of calcium pantothenate, of pyridoxine, and of mixed tocopherols—yet there is no evidence that man is ever deficient in these substances or is benefited by additional amounts. So why should they be added to vitamin preparations sold to the public? Their use in investigative medicine and experimental nutrition is one thing, but dispensing them to the public is another matter.

There is excellent evidence that inadequate nutrition does impair health, that it may cause specific diseases, and that it may predispose and aggravate other diseases. There is also good evidence, not only with experimental animals but with man, that really "excellent nutrition" over generations does result in marked improvement in general health, in greater resistance to disease, and in better physical fitness. But vitamins are only part of nutrition, and there is no evidence that man will become less fatigued, experience any fewer colds, or have more general resistance to disease by consuming "extra" amounts of various vitamins. May I repeat, good nutrition comes from a wide choice and a wide variety of wholesome food, not from a poor diet supplemented with vitamin and mineral preparations.

Let us examine briefly the recent claims that a large portion of our population is malnourished. These have generally resulted from various dietary surveys conducted on sizable groups of people in various parts of the country. In these studies it has generally been found that a large percentage of the subjects were consuming one, or generally several, nutrients in amounts less than those advised by certain dietary recommendations—generally recommendations based on very inadequate evidence, recommendations set at a level thought to be desirable for optimum health and well-being, and recommendations almost identical with those made in this paper. The implication has developed from these survey studies that a third, or a half, or two-thirds of the population are malnourished, and consequently not in the best of health. But seldom in any of these studies was evidence obtained concerning the status of health. True, a large majority of the people were malnourished, in comparison with certain recommended dietary allowances, but I do not believe there is evidence that any individual or group of individuals has impairment of health to any measurable degree, if they receive 50 mg. of ascorbic acid rather than 75; if they receive 1.5 mg. of riboflavin rather than 2.7, and so forth. But on the other hand no one has proved, as far as I know, that at these lower levels one enjoys as good health as at the higher levels. Do not misunderstand me—I do not feel that the recommended dietary allowances of the Food and Nutrition Board are not a good thing. They definitely are. There was a positive need for a set of dietary allowances supported by an authoritative group of individuals. They are a goal for optimum nutrition. They are subject to revision on sound experimental evidence, and they are an excellent guide

for preventive and therapeutic nutritional therapy. They are what they are entitled—"recommended dietary allowances." But it is certainly not sound to imply any degree of ill health solely on the basis of not meeting one or more of these recommendations.

There have been attempts in recent years to appraise the nutritional status of individuals by laboratory methods and special instrument methods. By the latter I refer specifically to the use of the slit lamp or biomicroscope for observing ocular changes in riboflavin and vitamin A deficiency, tongue changes in niacin deficiency, and gum changes in ascorbic acid deficiency. Literally hundreds of investigators have made studies of the plasma ascorbic acid, but there is no evidence that an individual with 0.4 mg. per cent ascorbic acid is any different from the viewpoint of health than one with 0.6 mg., a figure generally given as a desirable plasma level; it is thus not sound to say or imply that individuals with 0.4 mg. ascorbic acid are malnourished. The plasma ascorbic acid appears to be a measure of nutritional adequacy but not of inadequate nutrition. More recently ascorbic acid estimations have been done on white blood cells and here it appears that one gets a measurement of inadequate nutrition.

The vitamin A and carotene concentration in the blood can be estimated with reasonable accuracy and ease; but their interpretation in terms of health is most unsatisfactory, and there is no sound evidence to say that a person with 70 I.U. of vitamin A differs in health or well-being from a person with twice that concentration of vitamin A in the blood.

Corneal vascularization as a morphologic manifestation of riboflavin deficiency was first observed in the rat. Shortly thereafter it was observed in five or six other conditions and hence by itself cannot be accepted as a specific sign of riboflavin deficiency. The use of the biomicroscope in observing ocular changes in vitamin A deficiency, and tongue and gum changes in early niacin and ascorbic acid deficiency, is definitely in the investigative stage. It is one thing to observe and describe morphologic changes, and it is entirely another matter to show that these changes are the result of inadequate nutrition. Even response to specific therapy is not acceptable proof when it is necessary to continue the therapy for periods of a month or more. This particularly applies to observations on tissues such as the conjunctiva, tongue, and gums which are so readily subjected to minor infections and trauma.

There have been a number of classic investigations giving evidence

of the importance of improved nutrition on health, and I should like to mention briefly a few of these. Thus Robert McCarrison[2] in studies on two tribes in India found unmistakable evidence of the value of superior nutrition. In one of his papers he says: "For some nine years of my professional life, my duties lay in a remote part of the Himalayas where there are located several isolated races far removed from the refinements of civilization. Certain of these races are of magnificent physique, preserving until late in life the characteristics of youth; they are unusually fertile and long lived, and endowed with nervous systems of notable stability. . . . These people live on a very frugal diet, apricots, vegetables, goat's milk and butter—whole grains and meat only on feast days."

Then McCarrison studied a tribe in the south of India where the diet for generations had consisted of polished grains, vegetable fats, little milk, no meat, and few vegetables. The stature of this tribe was stunted, illness was common, mortality high. Now obviously there were genetic differences between these people, and environmental factors other than nutrition. But following his observations of these two tribes, McCarrison took a thousand albino rats and fed them for two and a half years on a mixed diet representative of one tribe. Another thousand rats were fed the diet of the other tribe. The differences found were even more striking with the rats than they had been between the tribes. It is of interest that this classic experiment was repeated on rats only a year ago by another investigator, and essentially the same results were obtained.

Orr and Gilks[3] conducted a study of two South African tribes with a view to possible improvement of physical efficiency through improved diet. These tribes live in regions which do not differ as to climate and agricultural possibilities. The adult males of one tribe average 5 inches taller and 23 pounds heavier than corresponding subjects in the other tribe. Muscular strength was found by dynamometer tests to be 50 per cent greater in one tribe. There were marked differences in the height and weight of the women of the two tribes. But the most striking differences occurred among the children. Of the children up to 8 years of age, both girls and boys, three-fourths in one tribe were graded as in good physical condition; in the other tribe only one-fourth were graded in good physical condition. Skeletal deformities, dental caries, spongy gums, anemia, diseases of the skin, and tuberculosis were rare in one tribe, most common in the other.

There were undoubtedly genetic differences between these peoples

but there were also significant dietary differences. One tribe consumed large quantities of milk, meat, and blood. The other tribe, while they raised large herds of goats, treasured them as wealth—not as food. They lived mostly on cereals and roots.

The classic study of Dr. Correy Mann[4] on English schoolboys should certainly be mentioned in any discussion dealing with nutrition and improved well-being. The experiments were carried out over a four year period on approximately 200 boys of 6 to 10 years of age. They show clearly the value of extra milk in improving health on diets which were thought to fulfill all nutritional needs. Those on the best diet —the basal diet plus a pint of milk per day—gained approximately 7 pounds per year as compared with 4 pounds per year on the control diet. In height there was also an increased gain. Throughout the four year period there was striking improvement in general fitness, fewer upper respiratory infections and other illnesses, and improved mental capacity. Dr. Mann states that these factors are difficult to measure and evaluate, but emphasizes that an impartial observer had no difficulty in pointing out quickly which boys were receiving the improved diet.

For many years Sherman[5] and his students at Columbia have been doing long term studies with rats, which advance the principle of *the nutritional improvability of what some consider the normal.* These animal feeding experiments have been carried on for many generations and with a rigorous regard for exactness. The basal diet used by Sherman in these studies consisted of 1/6 dried whole milk and 5/6 ground whole wheat plus salt and distilled water. Such a diet reared rats successfully through several generations. But improvement in the diet by having only a larger proportion of milk, improved greatly what could be considered the normal for the rats receiving less milk. Rate of growth and efficiency of growth were increased, as were average size, time required to reach maturity, time of full adult capacity, vitality as indicated by success in the launching of successive generations, and actual length of life.

Two years ago Ebbs, Tisdall, and Scott[6] published their now well known paper on the influence of prenatal diet on the mother and child. "The prenatal diets of 400 women with low incomes were studied. One group found to be on a poor diet was left as a control, a second group on a poor diet was improved by supplying food during the last three or four months of pregnancy, and a third group, found to have

moderately good prenatal diets, was improved by education alone. During the whole course of pregnancy the mothers on a good or supplemented diet enjoyed better health, had fewer complications, and proved to be better obstetrical risks than those left on poor prenatal diets. The incidence of miscarriages, stillbirths, and premature births in the women on poor diets was much increased. The incidence of illness in the babies up to the age of six months and the number of deaths resulting from these illnesses were many times greater in the Poor Diet Group."

In the Journal of Obstetrics and Gynecology for July 1943[7] is a report of some of the nutritional studies that the Harvard School of Public Health has conducted on the growth and development of the well child. These investigations are unusually significant in that they go back over a period of 12 years. All of the children in the study, of which there were originally 324, have actually been studied from birth, and before birth by antepartum studies on the mother. The complete studies include not only detailed and carefully conducted nutrition histories, but obstetric, pediatric, roentgenologic, dental, anthropometric, psychologic, and some laboratory studies.

This recently published work on 216 women and their infants, using the oldest sibling in each family, has shown a statistically significant relationship between antepartum diet and the condition of the infant at birth. In the 216 cases studied, every stillborn infant, every infant who died within a few days of birth, with the exception of one, the majority of infants with marked congenital defects, all premature and all "functionally immature" infants, were born to mothers whose diets during pregnancy were inadequate. From this study it would appear that if the mother's diet during pregnancy is excellent, her infant will in all probability be in excellent physical condition.

As in the study of Ebbs, Tisdall, and Scott, a significant relationship was also found to exist between the prenatal diet and the course of pregnancy. The findings with regard to eclampsia were most striking. In these 216 women there were 29 cases of eclampsia of varying degree. There was no incidence of eclampsia in those women with good or excellent diets; most of the cases of eclampsia were in those on poor diets, a few in the fair diet group.

Thus in the few studies briefly mentioned, all but one of which were done on human subjects, there seems to be good evidence that improved nutrition over long periods results in better health. There is also good

evidence that good nutrition is of profound importance during pregnancy, both for the mother and for the health of her infant.

But let us recognize that there is not convincing objective evidence that "excellent nutrition" is really a factor of major importance in the ordinary diseases we see, and that the best of present day biochemical techniques and special instrument methods do not give specificity in diagnosis. Most of those who have responsibilities for the health of individuals question the actual importance of "excellent nutrition" as compared with what one might call "average nutrition" in the majority of patients seen. There are several reasons for this. Nutrition is a relatively new science. Medicine is much, much older. It takes time for new principles to be adopted—unless, and this is important, there is a finding of dramatic importance to a specific disease. Medical training and thought, and environment in the clinical sciences, are in terms of disease, diagnosis, pathology, bacteriology, and wishful hopes, or justly proud admiration of dramatic cures—not in terms of health, preventive medicine, of longtime results. Nutrition, even today, is inadequately taught in most medical and public health schools.

As positive measures of how nutrition may be of more help to medicine and hence to society, may I suggest the following:

1. Nutrition should be introduced into the medical and public health schools to an extent and in a manner comparable to its importance.

2. It would be well if more of our medical schools had in each of the four main departments—medicine, surgery, obstetrics, and pediatrics —an individual trained not only in this field but also in nutrition.

3. A really high grade nutrition clinic should be established in a few representative regions of the country, not as a separate clinic, but as a part of a good general medical clinic, a good obstetrical clinic, and a good pediatric clinic, so that the outpatient records of these clinics would have detailed nutritional histories, laboratory findings, and clinical findings, on repeated visits, and over extended periods. Frequently on the ward we have patients who have been seen repeatedly over a period of several years in the outpatient clinics, and careful nutrition records of the previous years would help in establishing any relation between nutrition and their present condition.

4. Attempts to study growth and development in the well baby from before birth, that is antepartum studies on the mother, and through infancy, childhood, adolescence, and adulthood should be encouraged.

These studies should combine the best in clinical observations, the best in laboratory procedures, and the best in nutritional techniques. And we must not expect to get the full answers too quickly—it will take time.

Nutrition means more than vitamins—it is the science of food and its relation to health, and as such it is inseparable from any concept of medicine. But for nutrition to be of greater value to medicine we must seek objective and sound information relating it to the etiology and therapy of the common diseases we see.

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